cerebellum, a spinocerebellar degeneration, spinal ataxia, Friedreich's ataxia, a cerebellar cortical degeneration, a multiple systems degeneration, a systemic disorder, Refsum's disease, abetalipoprotemia, ataxia telangiectasia, a mitochondrial multi-system disorder, a demyelinating core disorder, acute transverse myelitis, a disorder of the motor unit, a neurogenic muscular atrophy, anterior horn cell degeneration, amyotrophic lateral sclerosis, infantile spinal muscular atrophy, juvenile spinal muscular atrophy, Alzheimer's disease, Down's Syndrome, a diffuse Lewy body disease, senile dementia of Lewy body type, Wernicke-Korsakoff syndrome, chronic alcoholism, Creutzfeldt-Jakob disease, subacute sclerosing panencephalitis, Hallerrorden-Spatz disease or dementia pugilistica.

Amendments to the claims are indicated in the attached "Marked Up Version of Amendments" (pages i - ii).

REMARKS

Claims 1-3 are pending. Claim 3 has been amended to correct a typographical error. Support for this amendment can be found in the Specification on page 58, line 27. No new matter is added.

Second Supplemental Information Disclosure Statement

A Second Supplemental Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the IDS is respectfully requested.

Objection to the Specification

The Specification has been amended to indicate that the current application is a continuation application. The WEHI cytotoxicity data which the Examiner has objected to is not new matter. The data can be found in the Specification of parent application 09/133,119 on pages 173, line 12 to page 174, line 8. Applicants have merely moved the data in the application to a more appropriate location for clarity purposes. As such, Applicants request reconsideration and withdrawal of the objection.

Rejection of Claim 3 under 35 U.S.C. § 112, Second Paragraph

Claim 3 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claim 3 has been amended to correct the typographical error "myelitisa" to "myelitis" and to remove the repeated phrase "cerebellar disorder". Reconsideration and withdrawal of the rejection are requested.

Rejection of Claims 1-3 under 35 U.S.C. § 112, First Paragraph

Claims 1-3 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner questions the enablement of the Specification for lack of evidence of the ability of A2 or cA2 antibodies and fragments to cross the blood brain barrier. The Examiner states that the art teaches the blood brain barrier is " impermeable to antibodies". For support of the state of the art, the Examiner has supplied an Abstract of Pardridge *et al., Trends in Biotechnology*, 12:239-245 (1994). Applicants respectfully disagree.

Applicants' invention is directed to a method of treating neurodegenerative diseases comprising administering to a human at least one monoclonal anti-TNF antibody or TNF binding fragment thereof. Depending claims are directed in part to multiple sclerosis and other neurogenerative diseases. Page 59, line 23 to page 63, line 24 of the Specification details various methods of administration of anti-TNF antibodies. For example, on page 61, lines 18-25, the Specification details the therapeutic administration of anti-TNF peptides or antibodies with the use of a vehicle for delivery, including the use of liposomes. One skilled in the art upon studying the Specification would know how to make and use Applicants' invention for therapeutic administration.

The Examiner has supplied the Pardridge abstract for support indicating the art teaches the blood brain barrier is "impermeable" to antibodies. The Examiner further requires that

Applicants must also teach a delivery system for transport of the anti-TNF peptides and antibodies across the blood brain barrier (BBB). Applicants respectfully disagree.

Applicants have obtained the full cite of the article and have enclosed a copy in the Second Supplemental Information Disclosure Statement filed herewith (Reference AU12). Review of the full article, indicates that there are existing strategies known in the art for delivery to the brain of antibodies and these strategies include (1) neurosurgery-based strategies; (2) pharmacology-based strategies for small molecules; and (3) physiology-based strategies. (See, *e.g.*, page 240, second column, lines 6-8). One skilled in the art would readily apply one of these strategies for delivery, for example the use of liposomes, with pharmacology-based strategies. As shown above, Applicants described this use of a liposome delivery system in the Application as filed.

Further, Applicants respectfully disagree with the Examiner's absolute statement that the BBB is impermeable to antibodies. Enclosed are two articles (References AV12 and AW12) showing that antibodies can cross the BBB. Reference AV12, by Bard *et al.*, describes direct evidence of labeled amyloid antibodies peripherally administered entering the central nervous system and binding to amyloid plaques located in the brain. Bard *et al.* states "These results indicate that antibodies can cross the blood-brain barrier to act directly in the central nervous system and should be considered as a therapeutic approach for the treatment of Alzheimer disease and other neurological disorders". (See Abstract, page 916, lines 22-26). Additionally, the AV12 reference by Brok *et al.* describes a labeled monoclonal antibody traversing the BBB and binding to lesions on the brain, see Fig. 6, page, 6561 and page 6557, second column, line 41 to page 6558, first column, line 9. Both references demonstrate the ability of an antibody to cross the BBB without a specialized transport system. Also, the antibodies had a label on them, bulking up the size. Applicants antibodies are not labelled.

Lastly, U.S. Patent No. 6,015,557 by Tobinick claims the systemic administration of Applicants' antibody (infliximab) for treatment of neurological conditions. No additional drug delivery methods were required. The issued Tobinick claims, drawn to systemic administration of antibodies, are presumed valid for satisfying the patentability requirements including enablement. This same standard should be applied to Applicants' claimed invention.

In view of the above, Applicants have enabled one skilled in the art to make and use the invention. Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 1, lines 4 through 18 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

This application is a [divisional] continuation of U.S. Application 09/133,119, filed August 12, 1998, which is a divisional of U.S. Application Serial No. 08/570,674, filed December 11, 1995, which is a continuation-in-part of U.S. Application Serial No. 08/324,799, filed October 18, 1994, now U.S. Patent No. 5,698,195, issued December 16, 1997, which is a continuation-in-part of U.S. Application Serial Nos. 08/192,102, now U.S. Patent No. 5,656,272, issued August 12, 1997, 08/192,861, now U.S. Patent No. 5,919,452, issued July 6, 1999, and 08/192,093, all filed on February 4, 1994 which are continuations-in-part of U.S. Application Serial No. 08/010,406, filed January 29, 1993, now abandoned, and U.S. Application Serial No. 08/013,413, filed February 2, 1993, now abandoned, which is a continuation-in-part of U.S. Application Serial No. 07/943,852, filed September 11, 1992, now abandoned, which is a continuation-in-part of U.S. Application Serial No. 07/853,606, filed March 18, 1992, now abandoned, which is a continuation-in-part of U.S. Application Serial No. 07/670,827, filed March 18, 1991, now abandoned. Each of the above applications are entirely incorporated herein by reference.

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

3. (Amended) A method of Claim 1, wherein the TNF-mediated disease is selected from AIDS dementia complex, a demyelinating disease, multiple sclerosis, acute transverse myelitis, an extrapyramidal disorder, a cerebellar disorder, a lesion of the corticospinal system, a disorder of the basal ganglia, [a cerebellar disorder,] a hyperkinetic movement disorder, Huntington's Chorea, senile chorea, a drug-induced movement disorder, a hypokinetic movement disorder,

Parkinson's disease, progressive supranucleo palsy, a structural lesion of the cerebellum, a spinocerebellar degeneration, spinal ataxia, Friedreich's ataxia, a cerebellar cortical degeneration, a multiple systems degeneration, a systemic disorder, Refsum's disease, abetalipoprotemia, ataxia telangiectasia, a mitochondrial multi-system disorder, a demyelinating core disorder, acute transverse [myelitisa] myelitis, a disorder of the motor unit, a neurogenic muscular atrophy, anterior horn cell degeneration, amyotrophic lateral sclerosis, infantile spinal muscular atrophy, juvenile spinal muscular atrophy, Alzheimer's disease, Down's Syndrome, a diffuse Lewy body disease, senile dementia of Lewy body type, Wernicke-Korsakoff syndrome, chronic alcoholism, Creutzfeldt-Jakob disease, subacute sclerosing panencephalitis, Hallerrorden-Spatz disease or dementia pugilistica.